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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,110	07/24/2006	Yuri Bereznitski	21586P	9528

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EXAMINER	
COUGHLIN, MATTHEW P	
ART UNIT	PAPER NUMBER
1626	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,110	BEREZNITSKI ET AL.	
	Examiner	Art Unit	
	Matthew P. Coughlin	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 20-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,17,18 and 20* is/are rejected.

7)☒ Claim(s) *2-8, 10-16 and 21-25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/10/2009, 10/19/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 and 20-26 are pending in the application. Claims 1, 9, 17, 18 and 20 are rejected. Claims 2-8, 10-16 and 21-25 are objected to.

Information Disclosure Statement

The Examiner has considered the Information Disclosure Statement(s) filed on August 10th, 2009 and October 19th, 2006.

Response to Amendment

The amendment to the claims filed on July 24th, 2006 does not comply with the requirements of 37 CFR 1.121(c) because claim 19 is cancelled but the text of claim 19 still appears in the listing of the claims. See section 4(i) below. Amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c) which states:

> (c) *Claims*. Amendments to a claim must be made by rewriting the entire claim with all changes (*e.g.*, additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).
>
> (1) *Claim listing*. All of the claims presented in a claim listing shall be presented in ascending numerical order. Consecutive claims having the same status of "canceled" or "not entered" may be aggregated into one statement (*e.g.*, Claims 1-5 (canceled)). The claim listing shall commence on a separate sheet of the amendment document and the sheet(s) that contain the text of any part of the claims shall not contain any other part of the amendment.
>
> (2) *When claim text with markings is required*. All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter

must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn—currently amended."

(3) *When claim text in clean version is required.* The text of all pending claims not being currently amended shall be presented in the claim listing in clean version, *i.e.*, without any markings in the presentation of text. The presentation of a clean version of any claim having the status of "original," "withdrawn" or "previously presented" will constitute an assertion that it has not been changed relative to the immediate prior version, except to omit markings that may have been present in the immediate prior version of the claims of the status of "withdrawn" or "previously presented." Any claim added by amendment must be indicated with the status of "new" and presented in clean version, *i.e.*, without any underlining.

(4) *When claim text shall not be presented; canceling a claim.*

(i) No claim text shall be presented for any claim in the claim listing with the status of "canceled" or "not entered."

(ii) Cancellation of a claim shall be effected by an instruction to cancel a particular claim number. Identifying the status of a claim in the claim listing as "canceled" will constitute an instruction to cancel the claim.

(5) *Reinstatement of previously canceled claim.* A claim which was previously canceled may be reinstated only by adding the claim as a "new" claim with a new claim number.

Any future correspondence should not present the text of cancelled claim 19.

Claim Rejections - 35 USC § 112 -1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 9, 17, 18 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a crystalline anhydrate of claim 2, 3, 4, 5, 6, 7 or 8, a crystalline monohydrate of claim 10, 11, 12, 13, 14, 15 or 16, a toluene solvate of claim 21, 22, 23, 24, 25,

26 does not reasonably provide enablement for any crystalline anhydrate form (referred to polymorphs in this rejection) of the compound of formula I, any monohydrate of the compound of formula I, or any toluene solvate of the compound of formula I and does not reasonably provide enablement for the pharmaceutical compositions of claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) *Breadth of the claims* - The breadth of the claims includes all the polymorphic forms, monohydrated and toluene solvated forms of the compound of formula I.

(b) *Nature of the invention* - The nature of the invention is drawn to the chemical synthesis of solvates, hydrates and polymorphs and pharmaceutical compositions thereof.

(c) *State of the prior art* - The state of the art recognizes that the formation, composition and therapeutic activity of solvates, hydrates and polymorphs is unpredictable. The Federal Circuit (in *SmithKline Beecham Corp. v. Apotex Corp.*, 74 USPQ2d 1398, 1409

(Fed.Cir. 2005)) has recognized solvates and hydrates, i.e. solvates where the solvent is water, as examples of polymorphs or pseudopolymorphs:

> *"Polymorphs" are distinct crystalline structures containing the same molecules. These structural differences can affect various properties of the crystals, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon) .... [P]seudopolymorphs are often loosely called polymorphs ... Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a solvate, which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.*

While the Federal Circuit addresses the fact that particular physical properties of hydrates, solvates and polymorphs can be different from the parent compound, the state of the prior art also recognizes that pharmaceutical properties, such as dissolution (which affects a particular compound's ability to elicit a desired biological response), can also be significantly different in hydrates, solvates and polymorphs compared to the parent compound. Giron (*J. Therm. Anal. Cal.* **2001**, *64*, page 39, internal citations omitted) teaches that:

> *The effect of polymorphism on bioavailability or toxicity is the most important consequence for drug substances if the bioavailability is mediated via dissolution. For the most famous case of chloroamphenicol palmitate, the active polymorph is not the thermodynamical [sic] stable one.*

Similarly, Souillac, et al., Characterization of Delivery Systems, Differential Scanning Calorimetry, pages 217-218 (in Encyclopedia of Controlled Drug Delivery, 1999, John Wiley & Sons, pages 212-227), teach that different polymorphs of the same drug can have different therapeutic activity:

> *Because different polymorphic forms of the same drug exhibit significant differences in their physical characteristics, therapeutic activity from one form to another may be different. Studying the polymorphism of a drug and the relative stability of the different polymorphs is a critical part of pre-formulation development.*

With respect to Applicant's claim to pharmaceutical compositions containing hydrates, solvates and polymorphs, the state of the art with respect to the generation of formulations containing crystalline forms is complex. The preparation of pharmaceutical formulations can require milling, adding excipients, surfactants, etc. Giron (*J. Therm. Anal. Cal.* **2002**, *68*, page 342) teaches that:

> *The formation of solvates or hydrates followed by drying into an anhydrous form can be extremely critical for the drying upscale if several hydrates, several anhydrous forms and the amorphous state may occur. Furthermore, the drug substance may undergo transformation during milling. For the dosage form, solvate or hydrate formation may occur during granulation. Excipients may accelerate transformation changes during mixing, tabletting. From our experience these highly critical questions have to be addressed and resolved before the transfer from development to production.*

(d) *Level of one of ordinary skill in the art* - The artisans synthesizing Applicant's hydrates, solvates and polymorphs and pharmaceutical compositions thereof, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level (at least a B.S. degree) and/or skill in the art, as well as several years of professional experience.

(e) *Level of predictability in the art* - As mentioned in section (c), there is a large degree of uncertainty in predicting the properties of a hydrate, solvate or polymorph given only the properties of the parent compound. There is no predictability in determining that a hydrate, solvate or polymorph will possess the same beneficial properties that make a given compound a drug candidate or similarly that a hydrate, solvate or polymorph will not possess the undesired properties that make a given compound unsuitable for pharmaceutical use.

More importantly, there is a severe lack of predictability in determining whether a given compound will even form a hydrate, solvate or polymorph and, if so, whether multiple polymorphic forms can exist. B. Rodriquez-Spong et al. (*Advanced Drug Delivery Reviews*, **2004**, *56*, page 263) teach that:

> *In general, scientists have yet to achieve a satisfactory degree of control over polymorphism and in particular there is no method to guarantee the production of even the most thermodynamically stable form of a compound. More problematic, and a commonly encountered task for pharmaceutical companies, is finding all forms of a compound that can exist under ambient conditions.*

(f,g) *Amount of direction provided by the inventor and Existence of working examples* - Applicant has provided sufficient guidance to make the particular hydrates, polymorphs and solvates of the dependent claims noted in the introduction of this rejection; however, the demonstration of particular solvates, hydrates and polymorphs does not reasonably apprise one of ordinary skill in the art as to the existence of additional polymorphs, solvates or hydrates. There is no guidance in the instant specification as to the generation and identification of additional solvated or polymorphic forms.

(h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - Given the state of the art and lack of predictability discussed in sections (c) and (e), undue experimentation is needed to practice the full scope of Applicant's instant invention especially in view of the lack of direction discussed in sections (f) and (g). Giron (*J. Therm. Anal.* Cal. 2002, *68*, page 344) teaches that a study of hydrates, solvates, and polymorphs requires a full research program and is well beyond that of routine experimentation:

> *The most challenging issue in the pharmaceutical industry is the proper study and characterization of polymorphs, and solvates [...]. Studies including crystallizations, equilibrations, granulating, tabletting have to be conducted in order to detect polymorphs and to characterize them. If properties (solubilities, dissolution, stability, and performance) are different, the impact on the dosage form has to be studied. Depending on the outcome, quantitative validated methods have to be developed and specification set for drug substance or for excipient or/and for the dosage form. Since changes may occur during processing or storage under the influence of mechanic stress, temperature, pressure and moisture, a proper study design has to be set and adequate methods have to be used.*

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (*In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary

skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for making and using any crystalline anhydrate form (referred to polymorphs in this rejection) of the compound of formula I, any monohydrate of the compound of formula I, or any toluene solvate of the compound of formula I, is clearly justified.

Notable Prior Art Not Cited in a Rejection

International Application Publication No. WO 03/104208 (published December 18th, 2003), International Application Publication No. WO 03/104207 (published December 18th, 2003), U.S. Patent No. 6,730,690 (PGPub US 20040048912 published March 11th, 2004) and U.S. Patent No. 7,179,802 (PGPub US 20040106664 published June 3rd, 2004) each by Olson et al. all teach the preparation of the instant parent compound; however, these is in sufficient guidance in the prior art to lead to the instantly claimed crystalline compounds.

Allowable Subject Matter

Claims 2-8, 10-16 and 21-25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew P. Coughlin whose telephone number is (571)270-1311. The examiner can normally be reached on Monday through Thursday from 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Matthew P. Coughlin/
Examiner, Art Unit 1626

/Rebecca L Anderson/
Primary Examiner, Art Unit 1626